# TITLE PAGE

**Information Type:** ViiV Healthcare Epidemiology Study Protocol

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| **Title:** | Post-marketing safety analyses for multiple marketed products in collaboration with the D:A:D study |

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| **Compound Number:** | GI265235, GSK2285967, GSK587048, GSK586135, UK427857, GW433908 |
| **Development Phase** | IV |
| **Effective Date:** | [DD-MM-YYYY] |
| **Subject:** | Post-marketing safety, Ziagen®, Kivexa®, Trizivir®, Combivir®, Celsentri®, Telzir® |

**Author(s):**

1. PPD
2. PPD ViiV Healthcare
3. PPD ViiV Healthcare
4. PPD
5. PPD
6. PPD
PPD

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| ADM | AIDS-defining malignancy |
| AEs | adverse events |
| AIDS | Acquired Immune Deficiency Syndrome |
| ALT | alanine transaminase |
| ARV | antiretroviral |
| AZT | zidovudine |
| cART | combination antiretroviral therapy |
| CLEE | chronic liver enzyme elevation |
| CV | cardiovascular |
| D:A:D | Data collection on Adverse events of anti-HIV Drugs |
| ESLD | end-stage liver disease |
| ESRD | end-stage renal disease |
| EU | European Union |
| HBV | hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICP | invasive cardiovascular procedure |
| MI | myocardial infarction |
| NADM | non-AIDS-defining malignancy |
| PYRS | person years |

## Trademark Information

| Trademarks of ViiV Healthcare and the GlaxoSmithKline group of companies |
|---|
| Ziagen® |
| Kivexa® |
| Trizivir® |
| Combivir® |
| Celsentri® |
| Telzir® |

| Trademarks not owned by ViiV Healthcare and the GlaxoSmithKline group of companies |
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## 2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

**MARKETING AUTHORISATION HOLDER**

ViiV Healthcare UK Limited

**Sponsor Legal Registered Address:**

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

**SPONSOR SIGNATORY:**

| | |
|---|---|
| Vani Vannappagari<br>Primary Author/ Project officer | **Date** |
| Harmony Garges<br>VP, Global Medical Sciences | **Date** |
| Nassrin Payvandi<br>VP, Safety and Pharmacovigilance | **Date** |

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: Caroline Sabin

Investigator Signature | Date

Investigator Name: Lene Ryom

Investigator Signature | Date

Investigator Name: David Kamara

Investigator Signature | Date

Investigator Name: Camilla Hatleberg

Investigator Signature | Date

# 3. ABSTRACT

ViiV Healthcare's pharmacovigilance strategy for the mature product portfolio is to monitor for long term safety of the products. This strategy is also included in the European Union (EU) Risk Management Plans for the products. To meet these regulatory commitments for Ziagen® (Abacavir), Kivexa® (Abacavir/lamivudine), Trizivir® (Abacavir/lamivudine/Zidovudine), Combivir® (Zidovudine/lamivudine), Telzir® (Fosamprenavir) and Celsentri® (Maraviroc), ViiV Healthcare in collaboration with the Data collection on Adverse events of anti-HIV Drugs (D:A:D) team, is conducting drug specific analyses of long term safety outcomes.

**Objectives:**

1. To describe any safety issues that arise among hepatically-impaired individuals exposed to Abacavir (ABC) containing products (Ziagen®, Kivexa®, Trizivir®) or Telzir®.
2. To determine the risk of carcinogenicity following exposure to Ziagen®, Kivexa®, Trizivir® and Combivir®.
3. To determine the risk of hepatotoxicity and ischaemic cardiac events following exposure to Celsentri®.
4. To determine the risk of hepatotoxicity and ischemic cardiac events in those exposed to Telzir®.

This will be a retrospective analysis of prospectively collected data from the D:A:D study which contains data from nearly 50,000 HIV-positive patients from 11 individual cohorts.

# 4. AMENDMENTS AND UPDATES

| Amendment or update no | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| <1> | <Date> | <Text> | <Text> | <Text> |
| <2> | <Date> | <Text> | <Text> | <Text> |
| <n> | <Date> | <Text> | <Text> | <Text> |

# 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Protocol Draft | 15-March-2017 |
| Registration on the EU PAS register | 27-April-2017 |
| Start of data analysis | 28-April-2017 |
| Draft report of study results | 30-June-2017 |
| Final report of study results | 15-August-2017 |

# 6. BACKGROUND AND RATIONALE

## 6.1. Background

The D:A:D study has been investigating potential antiretroviral (ARV) drug toxicities since 1999 and is a multi-national collaboration made possible due to the pre-existence of several large well-established HIV cohorts in Europe, Australia and the United States. As of August 1st, 2016, the D:A:D cohort consisted of nearly 50,000 HIV-positive individuals with an accrued follow-up time of nearly 470,000 person years (PYRS) of follow-up from 11 individual cohorts.

Since the D:A:D study has been running, the cohort has developed a rigorous study methodology which includes the adoption of study-wide case-definitions, robust and reliable event ascertainment, central classification of key events (with the input of external experts), extensive data monitoring and a robust approach to statistical analyses. Over the years, the D:A:D study has also cooperated with and encouraged the wider research community to undertake confirmatory analyses and research on biological mechanisms. The long experience of investigating potential associations between adverse events (AEs) and ARV drugs has enabled the study to provide guidance on the routine use of ARV drugs in clinical practice.

Because of its observational nature, there are challenges with analyses of clinical endpoints which result from the multiple drug switches and the wide variety of ARV combinations in use at any time. Further complexities are introduced through the

necessity to adjust for potential confounders, and the need to consider the possibility that HIV and/or the immunodeficiency that results from this may also be an underlying or contributing cause of several outcomes. The aim of the D:A:D study has always been, and will continue to be, to explore clinically relevant associations between exposure to combination antiretroviral therapy (cART) and centrally validated clinical events in a timely manner while, as far as possible, taking into consideration the impact of both measured and unmeasured confounders.

## 6.2. Rationale

ViiV Healthcare's pharmacovigilance strategy for the mature product portfolio is to monitor for long term safety of the products. This strategy is also included in the European Union (EU) Risk Management Plans for the products. To meet these regulatory commitments for Ziagen® (Abacavir), Kivexa® (Abacavir/lamivudine), Trizivir® (Abacavir/lamivudine/Zidovudine), Combivir® (Zidovudine/lamivudine), Telzir® (Fosamprenavir) and Celsentri® (Maraviroc), ViiV Healthcare in collaboration with the D:A:D: team, is conducting drug specific analyses of long term safety outcomes.

# 7. RESEARCH QUESTION AND OBJECTIVE(S)

Specific Aims:

1. To describe any safety issues that arise among hepatically-impaired individuals exposed to ABC containing products (Ziagen®, Kivexa® or Trizivir®) and Telzir®.
2. To determine the risk of carcinogenicity following exposure to Ziagen®, Kivexa®, Trizivir® and Combivir®.
3. To determine the risk of hepatotoxicity and ischaemic cardiac events following exposure to Celsentri®.
4. To determine the risk of hepatotoxicity and ischaemic cardiac events in those exposed to Telzir®.

| | |
|---|---|
| **1. Ziagen®, Kivexa®, Trizivir®:**<br>Potential risk: Carcinogenicity, Ischaemic cardiac events and Use in patients with hepatic impairment | **2. Celsentri®**<br>Identified risk: Hepatotoxicity<br><br>Potential risk: Ischaemic cardiac events |
| **3. Combivir®**<br>Potential risk: Carcinogenicity | **4. Telzir®**<br>Identified risk: Ischaemic cardiac events , Hepatotoxicity and Use in patients with hepatic impairment |

# 8. RESEARCH METHODS

## 8.1. Study design

This is a retrospective analysis of prospectively (exposure data collected before outcome is known) collected data from the D:A:D study.

## 8.2. Study population and setting

**Aim 1:** All D:A:D participants who have evidence of co-infection with hepatitis B virus (HBV)/ hepatitis C virus (HCV) and/or chronic liver enzyme elevations (CLEEs) at the time of initiating one of the three treatments/combinations will be included. D:A:D collects data on alanine transaminase (ALT), AST, total bilirubin, platelet counts, albumin, creatinine, and haemoglobin and a host of other laboratory testing. Participants from cohorts that do not provide information on ALT levels will be excluded and CLEEs will be defined as in the recent D:A:D paper by Kovari et al. (1). The study population will therefore be split into three groups at the time of initiation of each treatment/combination: (i) those with HCV and/or HBV infection and no CLEE; (ii) those with no HCV and/or HBV but with CLEE; and (iii) those with HCV and/or HBV and CLEE. Due to the estimated small number of study participants with chronic hepatic impairment and/or CLEE, and the possibility that the antiretroviral drugs may themselves induce hepatic impairment or liver enzyme elevation, the groups will be defined at the time of first exposure to the treatment/combination and will not be updated if an individual's status changes (e.g. if his/her ALT levels fall or if the individual subsequently becomes co-infected with HCV/HBV). Participants whose first ALT level in the dataset post-dates the start of the treatment/combination will be excluded. Where possible, dosing levels will be captured for the hepatically-impaired individuals.

**Aim 2:** All D:A:D participants without a prior cancer at D:A:D study enrolment who are enrolled from cohorts that provide data on cancer incidence will be included. Individuals who have died or are lost-to-follow-up before the cohort-specific baseline date for cancer analyses (2004 onwards) will be excluded.

**Aims 3 and 4:** All D:A:D participants without liver impairment (hepatotoxicity includes end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and CLEE) or without a prior myocardial infarction (MI) at D:A:D study entry. Analyses of liver impairment will additionally exclude those from cohorts that do not provide data on ALT levels.

## 8.3 Variables

### 8.3.1. Exposure definitions

The D:A:D study does not capture information on specific co-formulations. Therefore, participants exposed to Trizivir®, Kivexa®, Ziagen® and Combivir® will be identified as follows:

**Trizivir®:** Any person whose current regimen includes ABC, lamivudine (3TC) and zidovudine (AZT), regardless of other drugs in the regimen.

**Kivexa®:** Any person whose current regimen includes ABC and 3TC but not AZT, regardless of other drugs in the regimen.

**Ziagen®:** Any person whose current regimen includes ABC but not 3TC or AZT, regardless of other drugs in the regimen.

**Combivir®:** Any person whose current regimen includes AZT and 3TC but not ABC, regardless of other drugs in the regimen.

This will ensure that at any point in time, individuals can only be assigned to one of the four combinations (although individuals may switch from one of the combinations to another over time). Due to the very small number of persons exposed to Celsentri® and Telzir®, exposure to these drugs will be considered as any exposure, regardless of other drugs in the regimen.

### 8.3.2 Outcome definitions

**Aim 1:** Safety events will include:

- Clinical liver events (ESLD or HCC)
- Any cardiovascular CVevent (MI, invasive cardiovascular procedures (ICPs), sudden cardiac death, or stroke)

- Diabetes
- Cancer
- End-stage renal disease (ESRD)
- Mortality events

**Aim 2:** Cancer events will include:

- Any malignancy
- Any AIDS-defining malignancy (ADM)
- Kaposi's sarcoma (men only)
- Non-Hodgkin's lymphoma
- Cervical cancer (women only)
- Any non-AIDS-defining malignancy (NADM)
- Lung cancer
- Anal cancer (men only)
- Hodgkin's lymphoma
- Head and neck cancer

**Aims 3 and 4:** Hepatotoxicity and ischaemic cardiac events will include:

- Clinical liver endpoint: ESLD/HCC
- Laboratory-defined liver endpoint: CLEE
- MI

- Composite endpoint of MI or sudden cardiovascular death

In addition, assessment for hepatotoxicity will aim:

- To estimate the incidence of cases of combined alanine aminotransferase (ALT) and total bilirubin liver chemistry test elevations
- To estimate the incidence of discontinuation due to liver chemistry test elevations among exposed treatment naïve and treatment experienced HIV patients
- To determine risk factors for liver chemistry test elevations

Hepatic dysfunction as indicated by liver chemistry tests (LCT) will include the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations:

- ALT elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))
- AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
- Alkaline phosphatase (ALP) elevations
- Total bilirubin elevations
- Albumin
- For hepatic disease additional data collected→ possible biopsy, fibroscan and signs of hepatic decompensation (Ascites, Hepatorenal syndrome, Spontaneous bacterial peritonitis, Hepatic encephalopathy grade 3 or 4, Oesophageal variceal bleeding)

## 8.4 Data sources

D:A:D is a prospective, observational multi-cohort study that focuses on the early recognition of AEs, amongst which are cardiovascular events, cancers, and liver and renal diseases that could result from HIV treatment with antiretroviral agents.

## 8.5 Study size

As of Merger 17, the study has captured data from 49,706 HIV-positive persons with a total follow-up of 467,477 PYRS from 11 different cohorts. Among this cohort, the study has information on 5372 deaths, 1191 MIs, 2794 cancer events (877 AIDS-defining, 1917 non-AIDS defining), 2002 new diagnoses of diabetes, 569 strokes, 432 ESLD and 131 ESRD events. As not all events will contribute to all planned analyses, some of the analyses may be based on relatively small group sizes and thus analyses may be descriptive.

## 8.6 Data management

A full manual of operations (MOOP) and Standard Operating Procedures for the D:A:D study can be accessed on the D:A:D website (http://www.chip.dk/Studies/DAD/Study-Documents). These provide full details of the data management procedures that are in place as well as formats for data submission.

### 8.6.1. Data handling conventions

See above.

### 8.6.2. Timings of assessment during follow-up

Patients are seen for D:A:D clinical assessment at least every 8 months (depending on clinical need). Each participating cohort submits an annual electronic dataset to the D:A:D Co-ordinating centre.

## 8.7 Data analysis

The analyses will be based on the 17th D:A:D data merger of August 2016.

**Aim 1:** As it is likely that these individual groups will be relatively small, analyses will be largely descriptive and will summarise any subsequent clinical liver events (ESLD or HCC) as well as any CV event (MI, ICPs, sudden cardiac death and stroke), diabetes, cancer, ESRD, or mortality events that occur.

**Aim 2:** Participants will be stratified according to their level of exposure to each of the four treatments/combinations (no exposure; 0-2 years; 2-4 years; 4-6 years; 6-8 years, 8-10 years and >10 years) and strata-specific event rates will be calculated for the following outcomes:

- Any malignancy
- Any ADM
- Kaposi's sarcoma (men only)
- Non-Hodgkin's lymphoma
- Cervical cancer (women only)
- Any NADM
- Lung cancer
- Anal cancer (men only)
- Hodgkin's lymphoma
- Head and neck cancer

These outcomes have been chosen as they have the largest number of events in the current dataset. Follow-up will be considered from the baseline date for the cancer analyses (the latest of D:A:D entry or the cohort-specific baseline date for cancer analyses) to the date of the first new cancer over prospective follow-up (for analyses of specific cancer types, follow-up will therefore be censored at the time of a competing cancer event).

Poisson regression will be used to estimate unadjusted relative rates for the different exposure categories. If the number of each event is sufficient we will additionally fit multivariable Poisson regression models with adjustment for age, gender (where appropriate), cohort, mode of HIV acquisition, ethnic group, calendar year, previous cancer, smoking status, HCV and HBV co-infection. Models will also include adjustment for other ARV drugs in the regimen (results will not be shown for these other drugs).

**Aim 3:** Participants will be stratified according to whether or not they have ever received, or are currently receiving, Celsentri®. As the total number of D:A:D study participants exposed to Celsentri® is small, and the duration of exposure is generally short, no further stratification will be undertaken for duration of exposure to the drug. Event rates will be calculated for the following outcomes:

- Clinical liver endpoint: ESLD/HCC
- Laboratory-defined liver endpoint: CLEE (as defined above)
- MI
- Composite endpoint of MI or sudden cardiovascular death

As the number of events is expected to be small, no formal analyses will be undertaken, although the characteristics of those experiencing these events will be summarised.

**Aim 4:** Analyses will be similar to those described for Aim 3, although there will be some scope to stratify exposure to Telzir® (as none, <2 years, 2-4 years and ≥4 years). If the number of events is sufficient, we will perform Poisson regression to calculate relative rates for the exposure strata before and after adjustment for basic confounders (age and gender). Due to the limited exposure to the drug, we are unlikely to have sufficient numbers of events to be able to perform adjustment for other confounders.

## 8.8 Quality control and quality assurance

Please see D:A:D Study MOOP for quality control measures (http://www.chip.dk/Studies/DAD/Study-Documents).

## 8.9 Limitations of the research methods

Whilst analyses will attempt to take account of any potential confounders, the observational nature of the study means that we are unable to rule out the possibility that unmeasured or unadjusted confounding may be present. This is particularly true of the proposed analyses which may include small numbers of participants and may be descriptive in nature. Thus, care should be taken when interpreting any findings to avoid making assumptions regarding causality.

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1. Ethical approval and subject consent

Participating studies have existing national and/or local ethical approval, and obtain informed subject consent where required within these approvals.

## 9.2. Subject confidentiality

This analysis will use previously collected, anonymized data. No personal identifying information will be provided.

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves retrospective analysis of previously collected data in an aggregate manner. There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product.

Therefore, a study specific pharmacovigilance plan will not be developed.

# 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 11.1. Target audience

The target audience includes regulatory and health authorities.

## 11.2. Study reporting and publications

Final study results will be included in safety and regulatory reports as appropriate. Study results can be published if the sample size is sufficient for detailed analysis.

# 12. REFERENCES

1. Kovari et al. Antiretroviral Drugs and Risk of Chronic Alanine Aminotransferase Elevation in Human Immunodeficiency Virus (HIV)-Monoinfected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Open Forum Infect Dis. 2016 Jan 21; 3(1).